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DEPARTMENT OF HEALTH & HUMAN SERVICES
PURGED CAA 10/13/99

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

SEP 7 1999
VIA FEDERAL EXPRESS

WARNING LETTER

Dr. J. A. De Vries
President
European Medical Contract Manufacturing B.V.
Middenkampweg 17
6545 CH Nijmegen, The Netherlands

Dear Dr. De Vries:

We are writing to you because on March 15-18, 1999, an investigator from the Food and Drug Administration (FDA) collected information that revealed serious regulatory problems involving your Adcon-L device.

Under a United States Federal law, the Federal Food, Drug, and Cosmetic act (the Act), these products are considered medical devices because they are used to diagnose or treat a medical condition or to affect the structure or function of the body (Section 201(h) of the Act).

The above-stated inspection revealed that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation of this device are not in conformance with the Quality System Regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820. In legal terms, the product is adulterated within the meaning of section 501(h) of the Act, as follows:

1. Failure to employ appropriate statistical methodology where necessary to detect recurring quality problems, as required by 21 CFR 820.100(a)(1). For example, there is no requirement to assess the significance of in-process rejects or unanticipated test results, and the following rejects and results were not evaluated to determine if the failure mode/rate or results were consistent with process validation "baseline" data:

(1a) One "seal integrity" and two "pouch damage" defects for Adcon-L lot A9018N1 during 100% visual inspection;

(1b) One hundred "rejected [redacted] pouches" for Adcon-L lot A8069N1;

(1c) Two gel tube applicators rejected in packaging of Adcon-L lot A8069N1;

(1d) Five of seven Adcon-L samples from lot A8069N1 had bioburden results of ">900" cfu/g, and there was no documentation that the empty aluminum tubes identified for bioburden testing of the finished product were inadvertently not pre-sterilized before filling;

(1e) Result of 125 cfu/g for one bioburden (pre-sterilized tube) sample from lot A9006N1; lot A9018N1 had four bioburden sample levels between 1,200 to 4,000 cfu/g; and,

(1f) One hundred twenty (plus)[redacted] pouches rejected during pouching of Adcon-L lot A9006N1; and thirty-nine "seal integrity" rejects post-sterilization in lot A9006N1.

Your firm's March 23, 1999, response appears to be inadequate because it does not demonstrate that in-process rejects were consistent with process validation baseline data. In addition, you did not submit documentation to support your other statements.

Your firm's April 23, 1999, response to 1 appears to be inadequate because it does not demonstrate that the following are consistent with process validation baseline data:

1. one "seal integrity" and two "pouch damage" defects for Adcon-L lot A9018N1;

2. one hundred "rejected[redacted] pouches" defects for Adcon-L lot A8069N1;

3. rejecting two gels tube applicators that during packaging of Adcon-L lot;

4. bioburden results of ">900" cfu/g, and a proposed product bioburden level as high as[redacted]

5. not properly storing[redacted] used for in-process sampling of lot A8069N1 under[redacted] conditions;

6. results of 125 cfu/g for one bioburden (pre-sterilized tube) sample from lot A9006N1; and four bioburden sample levels between 1,200 to 4,000 cfu/g from lot A9018N1; and,

7. rejecting one hundred twenty (plus)[redacted] pouches during pouching of Adcon-L lot A9006N1, and rejecting thirty-nine "seal integrity" pouches post-sterilization for lot A9006N1.

In addition, your firm should submit data to support the acceptance of bioburden levels of 125 cfu/g to 4,000 cfu/g during production, and data to demonstrate that these bioburden levels do not raise the final product endotoxin levels above product specifications.

2. Failure to investigate the cause of nonconformities relating to product, processes, and the quality system, as required by 21 CFR 820.100(a)(2). For example,

(2a) During manufacture of Adcon L lot A8306N1:

(2a-1) Bioburden results were in excess of 300 CFU/g for Chryseomonas luteola for all seven samples tested. Investigation did not identify the origin of this organism, and no additional testing was done to determine if other organisms might have been present.

(2a-2) Sterility testing found two of 40 samples (one from each load sample size of 20) to be contaminated (Streptococcus faecalis, Enterobacter cloacae). The contract laboratory stated that the [redacted] cabinet used to perform the sterility testing was not equilibrated for at least [redacted] minutes before initiating sterility testing, but no analysis was done to determine if this was a sufficient explanation to invalidate the positive test results.

(2b) No investigation was done to determine the root cause of the following seal failures:

(2b-1) Gliatech complaint 0298A, dated July 13, 1998, relates to an opened/unsealed pouch from Adcon-L lot A8069N1-US1; investigation concluded that the complaint was valid and it was classified as a "Product Defect."

(2b-2) Gliatech complaint 01198A dated July 13, 1998, relates to an unopened/unsealed pouch from Adcon-L lot A8216Na-US02. Investigation concluded that the complaint was valid and it was classified as a "Product Defect."

(2b-3) Gliatech report dated October 7, 1998, states that Adcon-L lot A8229N1 -US01 failed due to inadequate pouch seals (25% failure rate).

(2b-4) Gliatech report dated October 8, 1998, states that Adcon-L lot A8252N1 had two dye test seal failures (8 samples tested).

Your firm's March 23 and April 23, 1999, responses to (2a-1) appear to be inadequate. Your firm should submit data to support the acceptance of theoretical bioburden levels or rationale for your theoretical bioburden levels of [redacted], and [redacted] and data to demonstrate that these bioburden levels do not raise the final product endotoxin levels above product specifications.

Your firm's March 23 and April 23, 1999, responses to (2a-2) appear to be adequate.

Your firm's March 23, 1999, general response to (2b) appears to be inadequate because the outer package maintains the sterility of the Adcon-L tube until it is introduced into a sterile field. There is a risk of infection if the health care provider does not identify the seal defect before product use, even if the product labeling includes a precaution against such use.

Your firm's March 23 and April 23, 1999, responses to (2b-1), (2b-2), (2b-3), and (2b-4) appear to be inadequate because you have not identified the root cause of the seal failures. In addition, you have not provided the results of the [redacted] and [redacted] from lots A8216N1-A8243N1.

3. Failure to identify the actions needed to correct and prevent recurrence of non-conformities relating to product, processes, and the quality system, as required by 21 CFR 820.100(a)(3). For example:

(3a) Corrective action for previously distributed product (i.e., same lots or lots processed under conditions causing the failures) was not initiated for the following:

(3a)(1) Gliatech complaint 0298A, dated July 13, 1998, relates to an opened/unsealed pouch from Adcon-L lot A8069N1-US1; investigation concluded that the complaint was valid and it was classified as a "Product Defect."

(3a)(2) Gliatech complaint 01198A, dated October 15, 1998, relates to a torn/open pouch from Adcon-L lot A8216N1-US02; investigation concluded that the complaint was valid and it was classified as a "Product Defect."

(3a)(3) Gliatech report dated October 7, 1998, states that Adcon-L lot A8229N1-US01 failed due to inadequate pouch seals (25% failure rate).

(3a)(4) Gliatech report dated October 8, 1998, states that Adcon-L lot A8252N1 had two dye test seal failures (8 samples tested).

(3b) Analytical Control Record for Adcon-L Gel Tubes requires that the clean room in which Adcon-L is manufactured be tested for environmental bioburden no more than [redacted] hours before starting manufacturing activities; results for lot A9018N1 show that test results were within specified limits. However, review of environmental test records found that the wall surface results obtained before production for this lot included an out of limit quantity of 284 CFU/100 cm^2 (limit is [redacted]). There is no documentation that corrective action was initiated in response to this out of limit result.

(3c) No corrective action is initiated unless non-conforming environmental test results relate to samples (walls, floors, work area, air) collected in the absence of cleanroom personnel; and there is no documented justification for not initiating corrective action when out of limit results are obtained for samples collected during routine processing.

Your firm's March 23 and April 23, 1999, responses to (3a)(1) and 3(a)(2) appear to be adequate.

Your firm's March 23 and April 23, 1999, responses to (3a)(3) and (3a)(4) are incomplete because you have not provided the evaluation of the [redacted] for lots A8216N1-A8243N1, and you have not indicated what corrective action you will take.

Your firm's March 23 and April 23, 1999, responses to (3b) appear to be inadequate because you have not indicated what the significance of environmental bioburden specifications are to product safety, and you have not demonstrated that lack of wall bioburden data has no adverse effect on product safety.

Your firm's March 23 and April 23, 1999, responses to (3c) appear to be adequate.

4. Failure to establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained; and failure to document these activities, as required by 820.72(a). For example:

(4a) The [redacted] sterilizer time control mechanism is not calibrated periodically, and there is no documentation justifying the lack of a calibration requirement.

(4b) Investigation of sterilization process profile deviations for Adcon-L syringes (non-US product) loads 6, 7, and 8 for lot A8299N1 concluded that the abnormal profiles were caused by a defective temperature probe. An empty chamber run after load 7 and before load 8 found no discrepancies. No evaluation was done or documented concerning whether previously sterilized product may have been adversely affected by this intermittent problem.

Your firm's March 23 and April 23, 1999, responses to (4a) appear to be adequate.

Your firm's March 23 and April 23, 1999, responses to (4b) are inadequate because you have not demonstrated that temperature and pressure were within specification for all product sterilized prior to the installation of the new power supply board, and that all product met [redacted] sterility test specifications. In addition, you have not provided English translations of SOPs M96091006 and "BIJLAGE PREVENTIEVE TECHNISCHE CONTROLE [redacted]".

5. Failure to provide for remedial action to reestablish calibration limits and to evaluate whether there was any adverse effect on a device's quality, when accuracy and precision limits are not met, as required by 21 CFR 820.72(b). For example:

(5a) Contractor-provided sterilizer temperature and pressure calibration results are not reviewed to determine if calibration was completed according to calibration requirements, and to determine if any remedial action for any previously sterilized product is necessary (a record of a calibration done by [redacted] the manufacturer of the sterilizer, does not include information as to the temperature measurements, and whether any adjustments were necessary).

(5b) Investigation of sterilization process profile deviations for Adcon-L syringes (non-US product) loads 6, 7, and 8 for lot A8299N1 concluded that the abnormal profiles were caused by a defective temperature probe. An empty chamber run after load 7 and before load 8 found no discrepancies. No evaluation was done or documented concerning whether previously sterilized product may have been adversely affected by this intermittent problem.

Your firm's March 23 and April 23, 1999, responses to (5a) are incomplete because you have not submitted the sterilizer temperature and pressure probe calibration data.

Your firm's March 23 and April 23, 1999, responses to (5b) are inadequate because you have not demonstrated that temperature and pressure were within specification for all product sterilized prior to the installation of the new power supply board, and that all product met [redacted] sterility test specifications. In addition, you have not provided English translations of SOPs M96091006 and "BIJLAGE PREVENTIEVE TECHNISCHE CONTROLE [redacted]".

6. Failure of the DMR (device master record) to include device specifications including appropriate drawings, composition, formulation, component specifications and software specifications, as required by 21 CFR 820.181(a). For example:

(6a) No bioburden specification has been established for Adcon-L [redacted] phosphate NF, or dibasic sodium phosphate USP.

(6b) No release specifications have been established for [redacted] used to cover Adcon-L gel before filling, [redacted] used for cleaning, and [redacted] used for sterilization qualification.

Your firm's March 23 and April 23, 1999, responses to (6a) appear to be inadequate because your firm has not submitted data to support a theoretical bioburden level of [redacted] and has not submitted data to demonstrate that a bioburden level of [redacted] would not raise the final product endotoxin levels above product specifications. In addition, there is no indication that the bioburden testing done on each incoming lot of aluminum tubes is done [redacted] or that the tubes are stored [redacted] until they [redacted] with Adcon-L.

Your firm's March 23 and April 23, 1999, responses to (6b) are incomplete because there is no English translation of the specifications for the [redacted] used for cleaning.

7. Failure to establish and maintain procedures to adequately control environmental conditions where those conditions could reasonably be expected to have an adverse effect on product quality; and failure to document those activities, as required by 21 CFR 820.70(c). For example,

(7a) There is no documentation that [redacted] used in the revalidation of the [redacted] sterilization cycle were stored at required freezer temperatures prior to use.

(7b) [redacted] powder requires storage at temperatures between 20°–25° C, but is being stored in an area where the temperature has varied from 9°–22° C.

(7c) Analytical Control Record for Adcon-L lot A8069N-US1 includes an air monitoring requirement using [redacted] no results are provided, and there is no documentation verifying that Gliatech eliminated this requirement.

Your firm's March 23 and April 23, 1999, responses to (7a) are incomplete because you have not provided documentation that the [redacted] used in the revalidation of the [redacted] sterilization cycle were stored at required [redacted] temperatures prior to use.

Your firm's March 23 and April 23, 1999, responses to (7b) are incomplete because you have not provided documentation that you are storing [redacted] at controlled temperature as defined by [redacted].

Your firm's March and April 23, 1999, responses to (7c) appear to be adequate.

8. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications, as required by 21 CFR 820.70(a). For example, there is no documentation:

(8a) confirming that the [redacted] Heat sealer procedure QA00083.1, issued December 18, 1998, has been implemented;

(8b) confirming the equipment settings and setup-related operations specified in the Heat Sealer procedure were used during manufacturing;

(8c) confirming the addition of Adcon-L ingredients;

(8d) confirming filtration of the Adcon-L solution through a [redacted] filter;

(8e) confirming the storage of the Adcon-L gel outside the refrigerator for between [redacted] hours before filling; and,

(8f) confirming that the 10 Adcon-L endotoxin test samples are randomly selected from [redacted] sterilization loads.

Your firm's March 23 and April 23, 1999, responses to (8a) are incomplete because they do not include documentation that the [redacted] Heat Sealer Procedure QA00083.1, issued December 18, 1998, has been implemented.

Your firm's March 23 and April 23, 1999, responses to (8b); (8c), (8d), (8e), and (8f) appear to be adequate.

9. Failure to validate a process with a high degree of assurance and to approve it according to established parameters, where the results of a process cannot be verified by subsequent inspection and test, as required by 21 CFR 820.75(a). For example, the [redacted] implement [redacted] cleaning procedure has not been validated.

Your firm's March 23 and April 23, 1999, responses appear to be incomplete because you have not included SOPs and validation data to support cleaning the [redacted] instrument with [redacted], and [redacted] prior to use.

10. Failure to document training, as required by 21 CFR 820.25(b). For example, there are no training records showing that individuals responsible for the operation of the [redacted] Heal Sealer have been appropriately trained for the procedure.

Your firm's March 23 and April 23, 1999, responses appear to be adequate.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA 483 issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

We acknowledge that you submitted to this office two responses, dated March 23, 1999, and April 23, 1999, concerning our investigator's observations noted on the form FDA 483. We have reviewed your response and concluded that it is partially inadequate. An evaluation of specific responses is entered after each one of the deviations listed above.

Given the serious nature of these violations of the Act, the Adcon-L manufactured by European Medical Contract Manufacturing may be detained without physical examination upon entry into the United States (U.S.) until these violations are corrected.

In order to remove the devices from this detention, it will be necessary for you to provide a written response to the charges in this Warning Letter for our review. After we notify you that the response is adequate, it will be your responsibility to schedule an inspection of your facility. As soon as the inspection has taken place, the implementation of your corrections have been verified, and you are notified that your corrections are adequate, your devices may resume entry into this country.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts.

Also, no requests for Certificates For Products For Export will be approved until the violations related to the subject devices have been corrected.

It is necessary for you to take action on this matter now. Please let this office know in writing within (15) working days from the date you received this letter the steps you are taking to correct the problem. We also ask that your explain how you plan to prevent this from happening again. If you need more time, let us know why and when you expect to complete your correction. If the documentation is not in English, please provide a translation to facilitate our review. Please address your response to:

Carol Arras
Office of Compliance
Division of Enforcement III (HFZ-343)
Center for Devices and Radiological Health
2094 Gaither Road
Rockville, MD 20850

If you have any questions about the contents of this letter, please contact Ms. Arras at the above address or at (301) 594-4659, or fax (301) 594-4672. You may obtain general information about all of FDA's requirements for manufacturers of medical devices by contacting our Division of Small Manufacturers Assistance at (301) 443-6597, or through the Internet at http://www.fda.gov.

Sincerely yours,

Larry D. Gleason for

Lillian J. Gill
Director
Office of Compliance
Center for Devices and
Radiological Health

Cc: